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Elevated HDL cholesterol levels are associated with osteoporosis in lung transplant candidates with chronic obstructive pulmonary disease

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KEYWORDS
Chronic obstructive pulmonary disease;
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Summary
Background: Osteoporosis is common in advanced COPD and worsens rapidly after transplantation, potentially impairing quality of life. Increased high density lipoprotein cholesterol (HDLc) has been observed in COPD and linked with osteoporosis in the general population. This association has not been previously examined in COPD.
Methods: We reviewed the records of 245 COPD patients referred for lung transplant evaluation. Osteoporosis was defined by either dual energy X-ray absorptiometry scan or use of osteoporosis medications. The presence or absence of osteoporosis could be ascertained in 152 subjects. Cholesterol values and other clinical variables were assessed for their association with osteoporosis.
Results: Clinical factors associated with osteoporosis included lower BMI [OR 0.81, 95% CI 0.73–0.90], higher HDLc [OR 1.04, 95% CI 1.02 to 1.07], and worse lung function. HDLc was an independent predictor of OP and demonstrated an inverse linear correlation with T-scores ($r = -0.21$, $p = 0.05$), which was stronger amongst males ($r = -0.45$, $p = 0.004$).
Conclusion: In COPD patients referred for lung transplantation, osteoporosis is highly prevalent. Raised HDLc levels are common in this group and are independently associated with OP.

Abbreviations: BMD, Bone mineral density; BMI, Body mass index; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; CVD, Cardiovascular disease; DXA, Dual x-ray absorptiometry; HRT, Hormone replacement therapy; OP, Osteoporosis; WHO, World health organization.

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Introduction

Advanced Chronic Obstructive Pulmonary Disease (COPD) is currently the second leading indication for lung transplantation in the U.S., accounting for 27% of transplants in 2008.[1] Lung transplantation in this population is often performed with palliative intent as it infrequently improves survival.[2,3] Quality of life usually improves after lung transplantation,[3,4] but can become severely reduced by osteoporotic fractures.[5] Vertebral fractures associated with OP can also significantly worsen lung function.[6,7] An accelerated loss of bone mineral density (BMD) and resultant increased risk of fractures is known to occur early after transplantation.[8,9] Furthermore, osteoporosis (OP) is a common and potentially serious complication of COPD, estimated to occur in 6%–69% of patients depending in part on the severity of illness.[10]

The basis for the increased risk of OP in COPD is not completely understood. Contributing factors include oral steroid use, physical inactivity, low BMI, reduced fat-free mass, tobacco exposure, nutritional deficiencies including vitamin D, advanced age, hormonal effects, and hypoxia.[11] However, COPD appears to be an independent risk factor for OP.[12]

Recent studies report a relationship between elevated high density lipoprotein cholesterol (HDLc) levels and osteoporosis in the general population.[13–17] Whether a relationship between HDLc and OP is present in COPD has not been previously studied, but unusually high HDLc levels have been reported in subjects with advanced COPD.[18,19] Tisi described 29 men with COPD in whom HDLc levels were compared to controls matched for age, obesity index, alcohol intake, smoking history, and race. Mean HDLc values were significantly elevated in the COPD subjects at 72 $\pm$ 4 mg/dl vs. 54 $\pm$ 3 mg/dl for controls.[19] While Tisi's data found no correlation between HDLc and hypoxia, Seishma compared 20 subjects with mixed lung disease including emphysema, pulmonary fibrosis, and cystic fibrosis against controls and found HDLc levels differed from controls only in the subjects with hypoxemia.[18] We reviewed data from a cohort of advanced, primarily hypoxemic, COPD patients evaluated for lung transplantation to assess the relationship between HDLc with OP.

Methods

This study was approved by our institutional IRB. Consecutive COPD patients referred to our center for consideration of lung transplantation from 1995 to 2009 were screened. Two hundred and ninety cases were reviewed and 45 were excluded, yielding 245 records. Reasons for exclusion were no diagnosis of COPD in 7, an additional lung disease in 28 and inadequate data in 16.

OP was defined either by bone mineral density (BMD) T-score ≤ -2.5 via dual energy X-ray absorptiometry (DXA) scanning, or use of bisphosphonate, teriparatide, or calcitonin therapy. DXA scanning is performed routinely as part of the evaluation for lung transplantation, irrespective of risk factors for OP. This case definition differs from that suggested by the World Health Organization (WHO) of a T-score below -2.5.[20] T-scores represent standard deviations from peak BMD adjusted for race and gender, whereas Z-scores represent standard deviations from mean BMD for a cohort the same race, gender, and age as the patient. The WHO definition is an imperfect surrogate end point relating to fracture risk. The proportion of fractures attributable to OP based on the WHO definition of osteoporosis is modest, ranging from $<$10% to 44%.[21] Many experts now suggest case finding and treatment decisions be based on risk assessment using the newer WHO FRAX assessment tool which incorporates clinical risk factors with BMD assessments to generate an estimate of 10 year fracture risk.[22] While this was beyond the scope of the data available in this study, the addition of medication use in case definitions has been validated in many chronic conditions, including OP.[23,24] As OP medication use could be associated with increased clinical risk factors for fracture and could also affect the measured BMD, those subjects taking OP medications were considered as having OP regardless of T-scores. Analysis of T-scores included evaluating the lowest T-score reported regardless of location, consistent with current recommendations.[25] Using this definition of OP, determination as to the presence or absence of OP could be made in 152 (62%) and this group comprised the study cohort.

The following data were recorded: demographics, anthropometrics, pulmonary function, medical comorbidities, medications, fasting lipid profile values and DXA scan results. Cardiovascular disease (CVD) was defined as a history of congestive heart failure, stroke, peripheral vascular disease, or coronary artery disease (CAD) included in the medical history or found by coronary angiography performed at the time of transplant evaluation.

Statistical analysis

Continuous data are expressed as mean (SD or range), and categorical data are presented as counts and percentages. Univariate analyses were made by Student *t* test, Chi^2 test, and Fisher's exact tests as appropriate. Pearson correlation coefficient was used to assess the relationship between continuous variables. Several multiple linear regression models were built to assess the relationship between osteoporosis and variables found to be significant at the 0.1 level in univariate analyses or thought to be of clinical importance. Reverse stepwise regression modeling was performed with a *p*-value inclusion threshold of 0.2 to generate the final multiple regression models. Underlying modeling assumptions were checked graphically and regression diagnostics were performed to assess for collinearity. Analysis was performed using Stata Statistical Software, Release 10.0 (Stata Corporation; College Station, TX).

Results

Of the 152 subjects included in the analysis, 116 (76%) had osteoporosis. The diagnosis was based on a positive DXA scan in 69 (59%) and medication use in 66 (57%). Thirty six (31%) met both definitions. Ten patients (7%) with T-scores above -2.5 were taking bisphosphonates or teriparatide and were categorized as having OP. By study design, those

classified as not having OP were all on the basis of DXA scanning. Compared to the study cohort, the 93 patients screened in whom the presence or absence of OP could not be ascertained had a lower proportion of oral steroid use [24% vs. 44%, ($p = 0.004$)], higher FEV_1% predicted [27% vs. 22%, ($p = 0.003$)], and were much less frequently listed for transplantation [3% vs. 59%, ($p < 0.001$)].

DXA scan results were available in 111 (73%) of the cohort, Z-score reporting was available in 89 (59%). Of those with DXA scans, 69 (62%) had osteoporosis, and another 40 (36%) had osteopenia defined by T-scores of; ≤ -1. Only 2 had normal BMD (Fig. 1). Z-scores also demonstrated a considerably negative distribution (online supplement). There was no statistically significant difference in the prevalence of osteoporosis, T-scores, or Z-scores between genders. Table 1 lists the clinical characteristics of subjects with and without osteoporosis. The former group had lower BMI's, worse pulmonary function, and was less likely to be listed for transplant. Of subjects with T-scores ≤ -2.5, 41% were supplemented with calcium and vitamin D, 57% were receiving treatment with a bisphosphonate, calcitonin, or teriparatide, and 35% took nothing for bone health.

Oral steroids were being used by 48% of subjects in the OP group at the time of evaluation, compared with 31% in the no osteoporosis group ($p = 0.06$). Among those taking oral steroids, only 55% took calcium and vitamin D. Inhaled steroid use was similar in the two groups at 76% and 75%, respectively. Eleven percent of females in both groups were on hormone replacement therapy.

The prevalence of CVD, CAD and other comorbidities were similar, with the exception of a somewhat higher proportion of systemic hypertension in the OP group (Table 1). Invasive hemodynamic values were available in 101 patients and differed only by slightly lower right ventricular pressures in patients with OP (online supplement). Total cholesterol (TC) values were slightly higher in the OP group, but HDLc was considerably elevated, resulting in a lower TC/HDLc ratio. This relationship was not affected by statin use.

Clinical factors significantly associated with osteoporosis by univariate analysis included BMI, FEV_1 %predicted, DLCO %predicted, and HDLc (Table 2). BMI correlated strongly with T-scores (Fig. 2) and also correlated inversely with HDLc (Fig. 3). An inverse linear correlation was observed between HDLc and T-scores ($r = -0.21$, $p = 0.05$). Several multivariate models were examined to assess the associations between clinical factors and osteoporosis. Clinical factors examined included age, gender, BMI, HDLc, an interaction term between HDLc and gender, oral steroid use, FEV_1 %predicted, and DLCO %predicted. In both stepwise logistic regression and all other logistic regression models examined, only BMI and HDLc remained independent predictors of OP and contributed significantly to the final multivariate model (Table 2). As bisphosphonates have been shown to modestly increase HDLc levels,[26] the final multiple logistic regression model was repeated after exclusion of all patients using bisphonates with virtually identical results.

To examine the potential effect of increased BMI values in the subjects with osteoporosis complicated by vertebral fractures, the logistic regression model of HDLc and BMI as predictor variables for OP was repeated with progressively reduced BMI values in the subjects with osteoporosis to find the threshold for statistical significance. This threshold occurred at BMI values 1 point reduced from reported, with greater reductions resulting in p-values above 0.05 for the relationship between HDLc and osteoporosis.

We then examined the relationship between HDLc and OP in males and females separately. In the entire cohort, mean HDLc values were above normal in both men (64 ± 25 mg/dL) and women (84 ± 27 mg/dL). HDLc levels in females were unchanged when those using hormone replacement therapy (HRT) were excluded. In both gender groups, HDLc was higher in those with OP versus those without. Mean HDLc values were 72 ± 26 vs. 49 ± 14 mg/dL ($p = 0.002$) in males and 89 ± 27 vs. 69 ± 21 mg/dL ($p = 0.004$) in females, respectively (Fig. 4). The inverse linear correlation between HDLc and T-scores for the entire group was heavily influenced by a strong relationship among males ($r = -0.45$; $p = 0.004$) (Fig. 5). Similarly, Z-scores correlated to HDLc levels only in the males ($r = -0.41$; $p = 0.02$).

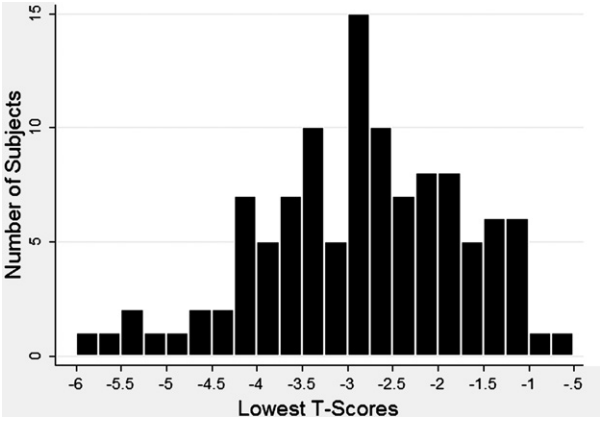

Figure 1 Histogram demonstrating distribution of T-scores in the study cohort. Osteopenia is defined as a T-score ≤ -1 and osteoporosis is defined as a T-score ≤ -2.5.

Discussion

Two important findings emerge from this study. First, the prevalence of abnormal bone density is extremely high in patients with advanced COPD referred for lung transplantation. Second, elevated HDLc levels are significantly and independently associated with osteoporosis in this population, particularly among males. This is the first study to assess the relationship between serum lipid values and osteoporosis in COPD.

Prevalence of osteoporosis and osteopenia

Our data show a nearly universal prevalence of osteoporosis or osteopenia in COPD lung transplant candidates. A prior study estimated the prevalence of osteoporosis or osteopenia in GOLD stage IV patients to be 75% with only 18% having osteoporosis.[27] This study used quantitative ultrasound rather than DXA scans and was limited to 28 patients in the stage IV group. A meta-analysis including 775 patients found a 35%

Table 1 Clinical characteristics by osteoporosis status.[a]

	Osteoporosis Absent ($n = 36$)	Osteoporosis Present ($n = 116$)	p-value
Age (yrs.)	55 (37–66)	57 (29–71)	NS
Gender (% Male)	42%	37%	NS
Race (% Caucasian)	92%	87%	NS
BMI	28.5 (21–47)	23.2 (13–35)	***
Smoking history (pk-yrs)	59 (5–120)	51 (1–200)	NS
Oxygen use (%)	86%	92%	NS
Sucessfully listed (%)	75%	54%	*
Transplanted (%)	33%	36%	NS
Comorbidities			
Cardiovascular disease (%)	36%	47%	NS
Significant CAD[b] (%)	26%	16%	NS
Diabetes (%)	17%	9%	NS
Hypertension (%)	33%	52%	*
Oral steroid use	31%	48%	0.06
Statin use (%)	28%	31%	NS
Lipid Profile ($N = 104$)			
Tot chol (mg/dL)	198 (147–300)	221 (122–413)	*
TG (mg/dL)	155 (50–452)	120 (34–779)	NS
LDL (mg/dL)	110 (40–185)	115 (41–237)	NS
HDL (mg/dL)	60 (31–104)	83 (30–167)	***
TC/HDL	3.7 (1.9–6.6)	2.8 (1.5–6.4)	**
DXA Scan Results ($N = 111$)			
Lowest T-scores	−1.7 (−2.47 to −0.7)	−3.3 (−5.8 to −1.1)	***
Lowest Z-scores	−0.9 (−2.2 to 0.1)	−2.16 (−4.1 to −0.1)	***
Lumbar T-score	−0.8 (−2.3 to 2)	−2.7 (−5.5 to 1.3)	***
Lumbar Z-score	−0.02 (−2.2 to 2.7)	−1.6 (−4.1 to 3)	***
Femoral neck T-score	−1.5 (−2.4 to −0.7)	−2.7 (−5.8 to −0.7)	***
Femoral neck Z-score	−0.5 (−1.7 to 0.3)	−1.6 (−3.9 to 0.3)	***
Trochanter T-score	−0.9 (−1.9 to 0.2)	−2.2 (−5.7 to 0)	***
Trochanter Z-score	−0.4 (−1.6 to 0.3)	−1.5 (−3.8 to 0.9)	***
Wards T-score	−1.7 (−2.47 to −0.7)	−3 (−5.5 to −1.2)	***
Wards Z-score	−0.02 (−1.6 to 1.5)	−1.3 (−3.3 to 0.8)	***
Total Hip T-score	−0.9 (−2.0 to 0.3)	−2.3 (−4.2 to −0.2)	***
Total Hip Z-score	−0.3 (−1.3 to 0.7)	−1.5 (−3.5 to 0.8)	***
Pulmonary Function ($N = 135$)			
FVC (% pred.)	55 (22–99)	47 (18–91)	*
FEV_1 (% pred.)	26 (10–73)	21 (6–47)	**
DLCO (% pred.)[c]	45 (13–99)	36 (9–76)	*
6MWD (m)[d]	279 (385–1556)	235 (257–1650)	0.09

*$p \leq 0.05$, **$p \leq 0.01$, ***$P \leq 0.001$.
[a] Data are presented as mean (range), or as percentages.
[b] $N = 84$. Defined as ≥50% stenosis in left main coronary, ≥70% elsewhere, or intervention performed.
[c] $n = 108$.
[d] $n = 59$.

pooled prevalence of OP in COPD and observed worse pulmonary function and lower BMI values in the subjects with OP.[10] The report included three studies involving COPD lung transplant candidates[10,27,28] in which the pooled prevalence of OP was 55%. This value is similar to our observation amongst subjects in whom T-scores were available in whom 62% had osteoporosis and 98% had osteoporosis or osteopenia.

HDLc and bone mineral density

Prior studies examining the relationship between HDLc and BMD have yielded conflicting results. A study of 13,970 young, highly active, Chinese subjects with a low prevalence of OP found no relationship between total body BMD and HDLc.[29] A large, epidemiologic study of relatively young, healthy subjects demonstrated a highly significant correlation between HDLc and BMD by DXA in univariate analysis which failed to persist after controlling for age, gender, and BMI.[30] A prospective study of 173 postmenopausal women using highly selective selection criteria excluding most medical comorbidities and BMI values outside a narrow range similarly observed a correlation between HDLc and BMD which did not persist after controlling for age, BMI, caloric intake, and duration of menopause.[15] In contrast, a study of 913 men and women exhibiting a relatively narrow range of BMI found a relationship between HDLc and BMD which

Table 2 Logistic regression for osteoporosis.

Predictor Variable	OR	95% CI	*p*-value
Univariate Analysis			
BMI	0.81	0.73—0.90	***
FEV_1% Pred	0.95	0.91—0.99	*
DLCO% Pred	0.98	0.95—0.998	*
HDL	1.04	1.02—1.07	***
Oral steroid use	2.12	0.96—4.7	0.06
Age	1.04	0.99—1.1	NS
Female Gender	1.21	0.57—2.6	NS
Multiple Logistic Regression Model[†]			
HDLc	1.03	1.004—1.053	*
BMI	0.81	0.72—0.92	***

*$p \leq 0.05$, **$p \leq 0.01$, ***$P \leq 0.001$.
[†] Age, gender, an interaction term between HDLc and gender, oral steroid use, FEV_1 %predicted, and DLCO %predicted were examined and found not to contribute significantly in multivariate modeling.

persisted after, but was attenuated by, controlling for body composition.[16] Another study of 214 postmenopausal Japanese women found an association between HDLc and BMD which persisted after controlling for age, BMI, and body composition.[17] Adami reported two Italian cohorts totalling 982 primarily older subjects in whom HDLc correlated to BMD after controlling for age, BMI, and body composition.[13] Most recently, Buizert described a cohort of 1255 primarily elderly men and women in whom HDLc correlated to BMD, which persisted in the women after controlling for age, BMI, smoking, physical activity, alcohol consumption, hypertension, and diabetes mellitus.[14] Notably, the studies suggesting an association between HDLc and BMD included older subjects with more comorbidities.

A previously proposed mechanism to link bone and lipid metabolism stems from the observation that osteoblasts and adipocytes share a common bone marrow progenitor cell and an inverse relationship between the commitment of these bone marrow-derived mesenchymal stem cells to the adipocyte versus osteoblast lineage pathways.[14,31] Regulation of this process is complex and involves PPARγ as a key regulator of adipogenesis by promoting adipocyte differentiation from these stem cells as well as inhibiting osteoblast differentiation.[32] HDLc may influence this process by removing oxygenated derivatives of cholesterol from peripheral tissues. These oxysterols have been shown to function synergistically with bone morphogenic protein-2 to induce osteogenic differentiation.[33] Various lipoproteins, including HDL, have also been shown to exert direct regulatory effects on osteoblasts,[34] and osteoclasts.[35,36]

Leptin regulates bone formation in concert with the sympathetic nervous system and has complex effects which may lead to increased or decreased BMD.[31,37] Leptin regulates HDL metabolism,[38] is inversely correlated with HDLc and HDL apo-A1,[39,40] and promotes bone formation through effects on both osteoblasts, as well as osteoclasts.[41,42] Certain leptin gene mutations are associated with COPD,[43] and leptin levels are decreased in COPD in contradistinction to asthma in which they are elevated.[44,45] Therefore, low leptin levels may contribute to both increased HDLc as well as decreased bone mineral density.

Systemic steroids clearly decrease BMD and increase fracture risk,[46,47] and have been associated with higher levels of HDLc.[48] However, they do not explain all the excess risk for OP as evidenced by abnormal bone metabolism and density in patients with COPD without exposure to corticosteroids.[49] While 44% of patients in our study were taking oral steroids at the time of evaluation, information

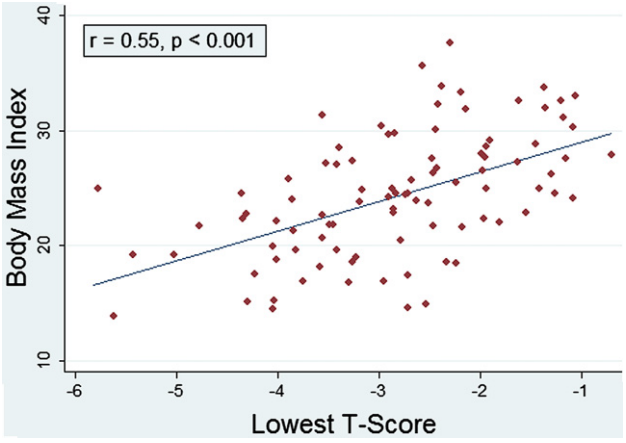

Figure 2 Pearson correlation between BMI and Lowest T-score by DXA scan.

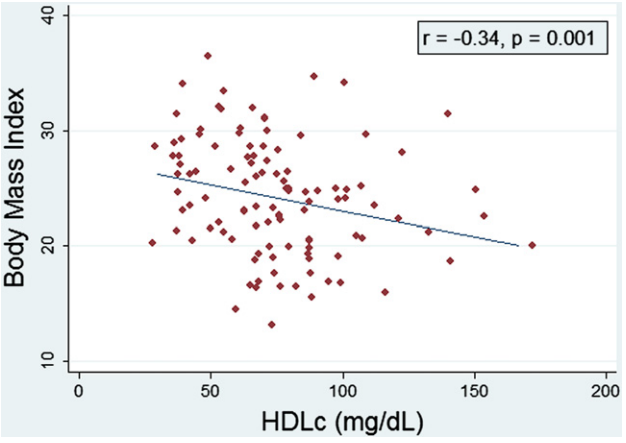

Figure 3 Pearson correlation between BMI and HDL cholesterol levels.

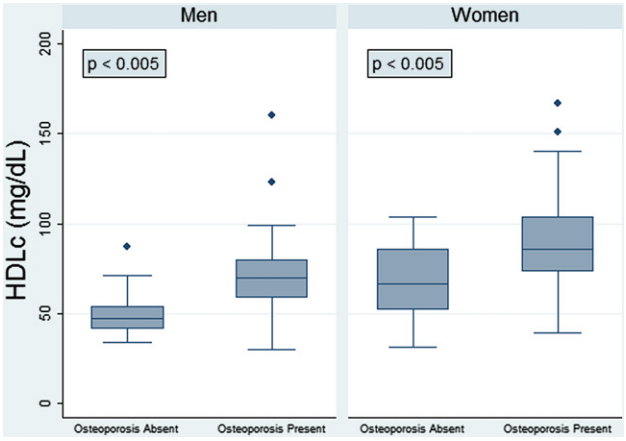

Figure 4 Box and whisker plot demonstrating HDL cholesterol levels by Gender and Osteoporosis Status. HDLc values differ by osteoporosis status in both men and women ($p < 0.005$).

pertaining to duration of use, dosing and intermittent use was not available and may explain the insignificant *p*-value of 0.06 comparing use between subjects with and without osteoporosis.

Hypoxia was nearly universal in our study subjects and may contribute to the association between elevated HDLc and osteoporosis in patients with COPD. Hypoxia affects HDLc metabolism via upregulation of plasma phospholipid transfer protein,[50] which transfers phospholipids between lipoprotein particles and alters HDLc subfraction patterns. Induced intermittent hypoxia has been shown to raise HDLc in patients with coronary disease.[51] Osteogenic activity of preosteocyte-like cells is impaired in a hypoxic environment,[52] and hypoxia in animal models leads to rapid bone resorption.[53] Hypoxia also decreases the mineralization potential of bone cells.[52] Whether these mechanisms apply to COPD patients is unproven, but the relatively low rates of OP noted in non-hypoxemic cohorts[54] lend credence to the association.

A mechanism that may explain the gender difference in the correlation between HDLc and BMD is male hypogonadism. Male hypogonadism can result in decreased bone

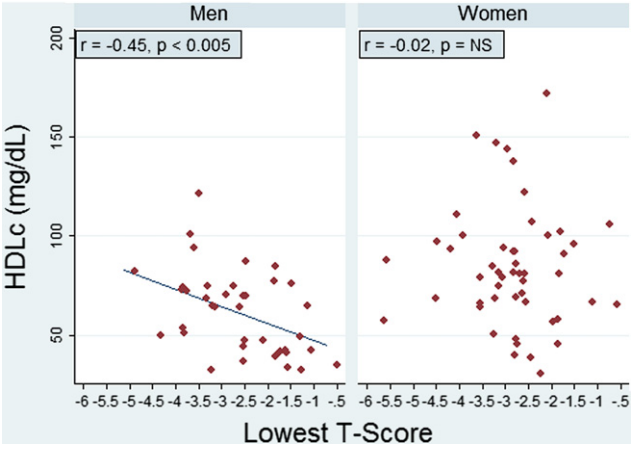

Figure 5 Pearson Correlation between lowest T-score vs. HDL cholesterol in males and females.

mineral density as well as elevated HDLc, and frequently complicates systemic disease.[55] While OP is generally more common in women, our cohort was unusual in that men demonstrated the same rates of OP as the women. The prevalence of hypogonadism in males with COPD has been estimated at 38%,[56] although the cohort from which this estimate was based had only moderate obstruction with minimal hypoxemia. Hypogonadism in COPD is more common with worsening hypoxemia, hypercarbia, steroid use, severity of obstruction, exacerbations, and increased inflammatory mediators such as IL-1, IL-6 and TNF-α.[55,57] Furthermore, glucocorticoid use reduces adrenal and gonadal hormones, including testosterone and estrogen.[47]

Study limitations

Due to the retrospective nature of this study, data pertaining to fractures, fat-free mass, calcium intake, testosterone, vitamin D, and parathyroid hormone levels were not available for analysis. Vertebral compression fractures in subjects with osteoporosis would result in increased BMI values. This would simultaneously weaken the correlation between BMI and OP and strengthen the association between HDLc and OP. However, our evaluation of the data suggest the effect of vertebral fractures in the osteoporosis group would have to exceed that sufficient to cause a mean reduction in BMI of 1 point, which would equate to between 1.2 and 1.5 inches reduction in the osteoporosis group. Vertebral fractures are common in severe COPD, as McEvoy showed in a cohort of 312 men with COPD in which 63% of patients using systemic steroids, and 49% of patients despite no exposure to oral or inhaled steroids were found to have vertebral fractures.[58] Yamaguchi described a difference of nearly an inch between subjects with and without vertebral fractures.[17] It is therefore likely that vertebral compression fractures contribute to the association between HDLc and OP independent of BMI, but do not account for it entirely.

Conclusions

In lung transplant candidates with advanced COPD, reduced bone mineral density is nearly universal. Low BMI is strongly related to osteoporosis. High HDL cholesterol levels are common in this population and are associated with osteoporosis independently of age, BMI, and severity of lung disease. This association appears stronger among males. Whether the elevated HDLc levels are directly involved in the pathogenesis of OP or simply reflect the effects of a common underlying process, such as hypogonadism, remains to be determined.

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None.

Conflict of interest

None.

Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2010.08.004

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